

CLINICAL RESEARCH

Control of an Outbreak of Human Parainfluenza Virus 3 in Hematopoietic Stem Cell Transplant Recipients

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Human parainfluenza virus 3 (HPIV3) infection can cause significant morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT). There are no standard guidelines for the prevention and control of HPIV3 in the outpatient setting. After 2 HSCT inpatients diagnosed with HPIV3 were noted to have had multiple recent HSCT outpatient clinic (OPC) visits, an investigation of policy and procedures in the HSCT OPC was undertaken, and active surveillance for respiratory viral illness was instituted in the at-risk HSCT population. Between July 19 and August 30, 2005, 13 patients were diagnosed with HPIV3 infection. Morbidity in affected patients was significant, and mortality was high (38.5%) and not affected by antiviral therapy. Molecular typing identified several genetically distinct groups of the hemagglutinin-neuraminidase gene of the 11 available isolates. Based on sequence relatedness among the isolates and the demographic and exposure history of the patients, in many of these cases HPIV3 infection likely was acquired in the HSCT OPC. The major infection control interventions were introduced between August 20 and August 24. An epidemic curve revealed that HPIV3 infection frequency peaked between August 17 and August 26, with no cases identified after August 30. Prompt attention and focus on infection control interventions were associated with a rapid decrease in the number of incident cases. Policies and procedures regarding patients with respiratory viral illnesses in HSCT OPC populations should be formulated and universally reinforced with HSCT clinic staff to prevent the spread of these infections.

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INTRODUCTION

Community-acquired respiratory viral infections are a significant cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT). Human parainfluenza virus 3 (HPIV3) has been associated with significant mortality, particularly when lower respiratory tract infections are identified [1]. In large transplantation centers, an incidence of HPIV3 infection as high as 2%-5% has been docu-

mented in patients undergoing HSCT [1-3]. HPIV-induced pneumonia has a mortality of 40%-50% in adult HSCT patients, and the infecting virus is predominantly type 3 [4].

Despite multiple reports detailing the infection control implications, morbidity, and mortality associated with HPIV3 infections in HSCT recipients, there are no consensus guidelines on the prevention and management of these highly contagious respiratory virus infections in severely immunocompromised hosts. Infection control strategies aimed at preventing virus acquisition are especially important given that HSCT recipients with HPIV3 infection may experience prolonged (up to 4 months) [4,5] or asymptomatic viral shedding [6]. Although ribavirin has been shown to be active against HPIV in vitro and in vivo, no controlled clinical trial (CCT) has established its efficacy in human HPIV disease [7-11]. For this reason, prevention of virus acquisition and transmission remains paramount.

Here, we describe an outbreak of 13 cases of HPIV3 infection in HSCT recipients over a 2-month period and the strict enforcement of the infection

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control procedures that were associated with containment of the infection.

METHODS

Patients and Setting

The Oregon Health & Science University in Portland is a large referral center for patients with hematologic malignancies that performs more than 120 adult allogeneic and autologous HSCTs annually. HSCT recipients treated in the inpatient setting are admitted to 1 of 3 different transplantation or oncology wards. All staff and visitors in these units are asked to adhere to strict hand hygiene procedures on entering the ward. All patients treated in the outpatient settings are seen in a clinic located in another building, across the street from the hospital. The layout of the OPC consists of a large waiting room, from which patients are directed to either a large open infusion center room or to 1 of 10 individual exam rooms. Before the study intervention, the patients were reminded by signs to practice hand hygiene, cover the mouth when coughing, and don a mask for respiratory viral symptoms; however, no organized, ongoing assessment of compliance with this practice was in place. Droplet precautions practiced in the outpatient setting before the investigation were usually limited to the patients who had obvious respiratory tract infections. Contact isolation was usually limited to patients colonized with vancomycin-resistant enterococcus. Routine nasal swabs or washings for respiratory viral screening were not performed in patients with symptomatic respiratory illnesses before implementation of the intervention.

Definitions

Upper respiratory tract infection (URTI) was defined as the presence of coryza, pharyngitis, sinusitis, and/or cough with or without fever and a clear chest radiograph. Lower respiratory tract infection (LRTI) was defined as the presence of wheezing, hypoxia, or pneumonia with a new chest radiographic opacity or low oxygen saturation.

Institutional policy for ill OHSU employees with patient contact (ill-provider policy) includes exclusion from duties including any contact with patients for 5 days after onset of respiratory symptoms. Compliance with this policy is not strictly monitored, however.

For patients in contact isolation, all health care providers and family members were required to don a gown and gloves before entering the room. For patients in rooms with droplet precautions in place, all health care providers and family members in close contact with the patient were required to wear a mask.

Isolation Procedures

In the 2 HSCT inpatients diagnosed with HPIV3 infection by bronchoalveolar lavage (BAL), a review of their recent outpatient history revealed multiple OPC visits in the preceding weeks. Based on this observation, the following policies and procedures were empirically undertaken in an attempt to assess the prevalence of HPIV3 in the HSCT OPC and to prevent further potential spread of the disease:

1. All adult patients in the bone marrow transplantation (BMT) center between early August and September 30, who had signs and symptoms of URTI or LRTI in the outpatient setting, underwent detailed clinical evaluation, and samples were acquired from URT or LRT washings. Patients with LRTI with new pulmonary abnormalities on computed tomography scan underwent BAL.
2. In the OPC, patients and family members were asked to wash their hands and were screened for acute respiratory illness on entry to the OPC (see 3). Symptomatic patients were immediately masked and placed in a private room with contact and droplet precautions, and a respiratory viral screening sample was obtained. Symptomatic family members were asked to remain in an area of the waiting room separate from the patients.
3. Detailed guidelines and scripts for phone and clinic triage were created for use by staff to question all patients, whether presenting by phone or in the clinic. Respiratory transmission information signs requesting that all patients, family members, and friends with respiratory symptoms should practice hand hygiene and don a mask immediately were posted just outside the clinic door, inside all outpatient units, and in the HSCT inpatient units.
4. Staff involved in patient care in the outpatient and inpatient settings were questioned about recent URTI or LRTI symptoms and signs. Adherence to the institutional ill-provider policy was made mandatory if any signs of URTI or LRTI were elicited.
5. Visitation by symptomatic family members was prohibited.
6. The decision whether to admit patients and treatment decisions were made by the HSCT provider team in consultation with the Infectious Diseases service.
7. Patients with documented HPIV3 were asked to adhere to strict hand hygiene policy, wear a mask for 1 month after active infection during all OPC visits, and were placed in private rooms for the same duration.

In the inpatient setting, in addition to the foregoing precautions, the following procedures were instituted:

1. HSCT inpatients with respiratory illness were isolated and screening respiratory viral samples obtained.
2. Family visitation was limited.

Virology Procedures

Nasopharyngeal washings obtained from all HSCT recipients with URTI symptoms and BAL for those with LRTI were submitted for viral testing. Shell vial cultures were performed on all specimens sent for viral testing. The shell vial cultures were screened at 24 hours using a pool of monoclonal antibodies (mAbs) to a panel of respiratory viruses (Diagnostic HYBRIDS, Athens, OH), including HPIV1-3, adenovirus, influenza A and B, and respiratory syncytial virus (RSV). If positive, the specimens were stained with the individual mAbs to identify the virus. If negative at 24 hours, the shell vial cultures were screened again at 48 hours.

The 11 HPIV3 isolates obtained during the outbreak period were sent blinded to the Centers for Disease Control and Prevention (CDC) for molecular typing. Reverse-transcription polymerase chain reaction (RT-PCR) and sequencing of nucleotides 1-424 of a variable region of the hemagglutinin-neuraminidase (HN) gene was performed as described previously [12]. Selected isolates were resequenced from new RNA extracts to confirm results. Nucleotide alignments were compiled using the Pileup program, Wisconsin package, version 11.1.2 for UNIX (Accelrys, San Diego, CA), and phylogenetic analysis was performed by maximum likelihood using PAUP* version 4.10 (Sinauer Associates, Sunderland, MA) [13].

Treatment of LRTI

Some patients with LRTI secondary to HPIV3 were treated with ribavirin (1-Beta-D-ribofuranosyl-1H-1, 2, 4-triazole-3-carboxamide). Ribavirin was administered by endotracheal tube for 18-24 hours/day as a continuous aerosol or i.v. The dosage for aerosolized ribavirin was 6 g/day for 5 days; for i.v. ribavirin, an initial loading dose of 33 mg/kg body weight was followed by 16 mg/kg every 6 hours for 4 days, then 8 mg/kg 3 times a day for an additional 3 days.

RESULTS

Identification and Demographic Data of Cases

Between July 21, 2005, and August 30, 2005, 13 HSCT recipients were diagnosed with HPIV3 infection. Of these 13 cases, 5 (38.5%) were inpatients and 8 (61.5%) were outpatients at diagnosis. Table 1 summarizes patient characteristics.

Molecular Analysis

Molecular typing of the HN gene of the 11 available isolates identified at least 3 genetically distinct groups (Figure 1). One group contained a single isolate obtained from the first recognized case (patient 1), who was transferred to the inpatient service from an outside facility 200 miles away; a second group contained 6 isolates with identical sequences (patients 2, 4-7, and 11); and a third group contained 4 isolates, 2 with identical sequences (patients 3 and 9) and 2 with unique sequences, differing from all others by 1 or 2 nucleotide substitutions. Isolates from 2 patients were unavailable because the patients were diagnosed at an outside facility and transferred to OHSU late in their course.

Exposure Analysis

The first case of HPIV3 infection was diagnosed on June 21, 2005. This patient was transferred from outside hospital for respiratory distress. BAL performed on the next day tested positive for HPIV3. The second case was identified 1 month later, on July 20, 2007, in the inpatient HSCT unit. Between August 1 and August 20, 2007, 7 more cases were identified, and the enhanced infection control policies were enforced starting on August 20.

Clinic visit charts and inpatient hospital room assignments were reviewed. Inpatient nosocomial transmission was not suspected in the majority of cases, based on the (1) lack of inpatient physical proximity, (2) prevalence of diagnosis in the outpatient setting, and (3) admission to the hospital after identification of established respiratory disease. Of the 11 cases in which HPIV molecular typing was performed, 10 patients had at least one potential shared exposure during a common clinic day in the preceding month with another infected patient, and most shared multiple clinical visits. A review in the context of the molecular analysis determined that the 5 patients with group 2 virus had 1-3 common clinic days with others in the group (June 14 and July 20, 22, 25, and 27). Of the 4 patients with group 3 viruses, 2 were seen on July 20 and 3 were seen on August 16.

Questionnaires given to clinic staff did not elicit any personal acknowledgment of respiratory signs and symptoms while at work during the outbreak period. However, multiple staff members did note that before the intervention period, several unmasked symptomatic patients and family members had been cared for in the open care area of the OPC.

Infection Control Interventions

The major infection control interventions were introduced between August 20 and August 24. An epidemic curve revealed that HPIV3 infection frequency peaked between August 2 and August 26 (Figure 2).

Table 1. Patient Characteristics

	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Age, years	42	29	65	32	58	48	65	49	40	55	56	52	72
Sex	M	M	F	M	F	F	F	M	M	M	M	M	M
Treatment type	MUD	MUD	Mini-MUD	MUD	Mini-MUD	MUD	Mini-MUD	MUD	MUD	MUD	MDS	Sibling allogeneic	Mini-MUD
Diagnosis	PH + ALL	CML	CLL	NHL	AML	AML	MM	CML	AML	NHL	MDS	NHL	AML
ECOG	3	3	1	2	2	1	2	3	3	2	4	2	1
Graft-versus-host disease	Chronic skin, lung, liver	None	None	Chronic lung, sicca syndrome	None	None	None	Chronic lung	Chronic lung, eye, skin	Chronic liver	None	Acute skin	Pretransplantation
Prednisone >20 mg	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	Yes	Yes	No
Duration of symptoms	5 days	Asymptomatic	24 hours	7 days	5 days	3 days	4 days	> 1 month	10 days	Unknown	1 month	24 hours	2-3 days
Time after treatment/engraftment status	3 years/+	14 days/-	6 days/-	2 years/+	17 days/+	48 days/+	25 days/+	8 months/+	4.7 years/+	132 days/+	38 days/+	45 days/+	Pretransplantation
Pulmonary status	History of Pseudomonas pneumonia 3/04, 8/04, 3/05; 2 L O ₂	O ₂ saturation 96% on RA; chest x-ray/computed tomography changes; crackles	O ₂ saturation 99% on RA	History of BOOP; O ₂ saturation 97% on RA	O ₂ saturation 90%-92% on RA	O ₂ saturation 99% on RA	O ₂ saturation 96% on RA	History of cytomegalovirus pneumonia +05; O ₂ saturation 97% on RA	Concomitant infection with C. gabraia, C. guilliermondii, MRSA (BAL)	On RA	Presented with rapid-onset respiratory failure before BAL; DAH with CMV + effusions	O ₂ saturation 95% on RA	O ₂ saturation 100% on RA
ALC	200	0	WBC 0.4	1000	200	400	500	1500	WBC 5.3	400	WBC 3.5	800	600
Ribavirin	i.v., HD, i.v. IG	No	Inhaled × 5 days, i.v. × 3 days	Inhaled × 7 days	Inhaled × 7 days	No	No	Inhaled × 7 days	No differential i.v. × 3 days	No	No differential i.v. × 7 days	No	No
Symptoms Outcome	LRTI Expired	LRTI Expired	LRTI Recovered	LRTI Expired	LRTI Recovered	URTl Recovered	LRTI Recovered	LRTI Recovered	LRTI Recovered	URTl Recovered	LRTI Expired	URTl Recovered	URTl Recovered

BAL, Bronchoalveolar lavage; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; AML, acute myelogenous leukemia; MUD, matched unrelated donor; MM, multiple myeloma; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma.

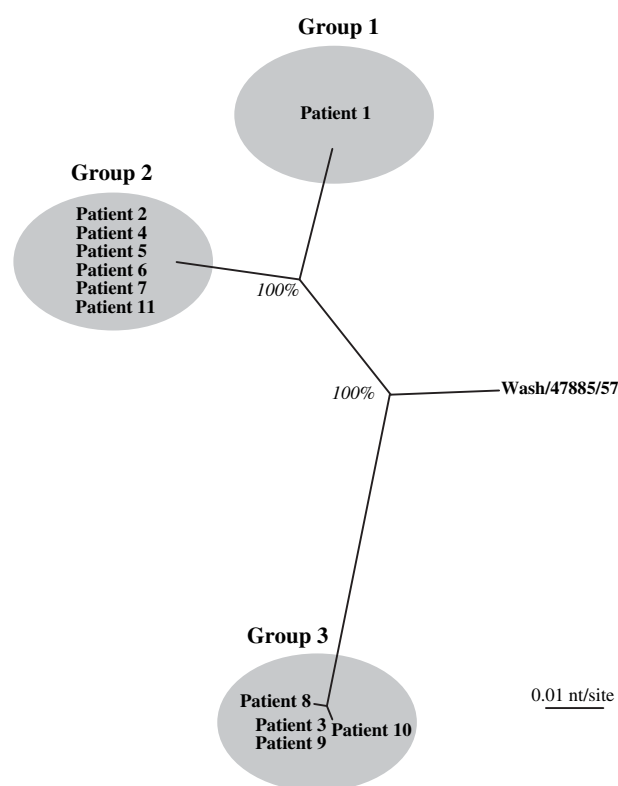


Figure 1. Maximum likelihood tree obtained from the nucleotide alignment of HPIV3 HN gene sequences (nt 1-424) from 11 patients. Three major clades are highlighted. Prototype strain Washington/47885/57 is included as an outgroup. Bootstrap values are indicated for selected nodes.

The final 4 HPIV3 cases were diagnosed on August 24, 26, and 30. Screening nasal washes were performed on symptomatic patients in the OPC until December, and no HPIV3 infection was identified after August 30.

Patient Outcomes

The overall mortality of patients diagnosed with HPIV3 was 38.5% (5/13). All of the patients who died had signs of LRTI, and 4 had been treated with inhaled ribavirin.

DISCUSSION

The spectrum of HPIV3 disease in HSCT recipients ranges from uncomplicated URTIs, characterized by rhinorrhea, pharyngitis, and coryza, to more severe LRTIs that may lead to pneumonia, respiratory failure, and death. The epidemiology of HPIV3 infection after HSCT is different from that associated with latent endogenous viral infections, such as cytomegalovirus (CMV) infections, in which the patient's serologic status and degree of immunosuppression play major roles in disease occurrence [13]. A retrospective analysis of cases has shown a correlation of HPIV3 infection with the type of transplantation

and the degree of immunosuppression [2]; however, the majority of cases of HPIV3 still are linked primarily to patient exposure to the virus, with these other factors likely contributing to individual patient susceptibility.

Viral transmission occurs by direct inoculation of contagious secretions from hands or of large particle aerosols into the eyes, nose, or, rarely, the mouth. The prolonged survival of HPIV3 on the skin, clothes, or other objects emphasizes the importance of fomites in the spread of nosocomial virus and of the critical importance of handwashing in controlling infection transmission [1,2,13-14].

In immunocompetent adults, this infection rarely causes significant morbidity or mortality. However, in HSCT recipients with established pneumonia, the mortality rate is very high, and no currently established treatment regimens have been shown to reduce it [1,15-17]. Because this disease is highly transmissible and is associated with significant morbidity, preventing exposure in this vulnerable population may be the most critical intervention to pursue. Aggressive infection control measures play a key role in preventing HPIV3 infections and their sequelae in these compromised hosts. This may be complicated by the fact that viral shedding may be either asymptomatic or prolonged [4-6]. Although there are guidelines regarding prevention of RSV and influenza, most practices concerning HPIV3 are based on data extrapolated from these other studies [14]. Consensus guidelines on prevention and management strategies for HPIV3 infections in severely immunocompromised patients are lacking.

In our cluster of 13 patients with laboratory-confirmed HPIV3 infection, the geographic proximity and molecular typing of the virus suggests that in many of the patients, virus acquisition likely was nosocomial and took place in the shared, open outpatient infusion area and clinic. Evaluation of the clinic environment and questionnaires to staff supported the plausibility of this finding. Before the outbreak, a number of patients and family members with URTIs had been present in the common area of the OPC infusion center, in close proximity to other patients without any isolation precautions. Active infection control interventions oriented toward strict limitation of patient-to-patient contact were associated with control of viral spread in a relatively short period.

Although the epidemic curve suggests control after intervention, it could be argued that the decrease in incident cases represented the natural progression and outcome of the disease as demonstrated by CDC's National Respiratory and Enteric Virus Surveillance System (NREVSS) regional HPIV3 surveillance data. However, studies from the Fred Hutchinson Cancer Research Center have shown that unlike in community

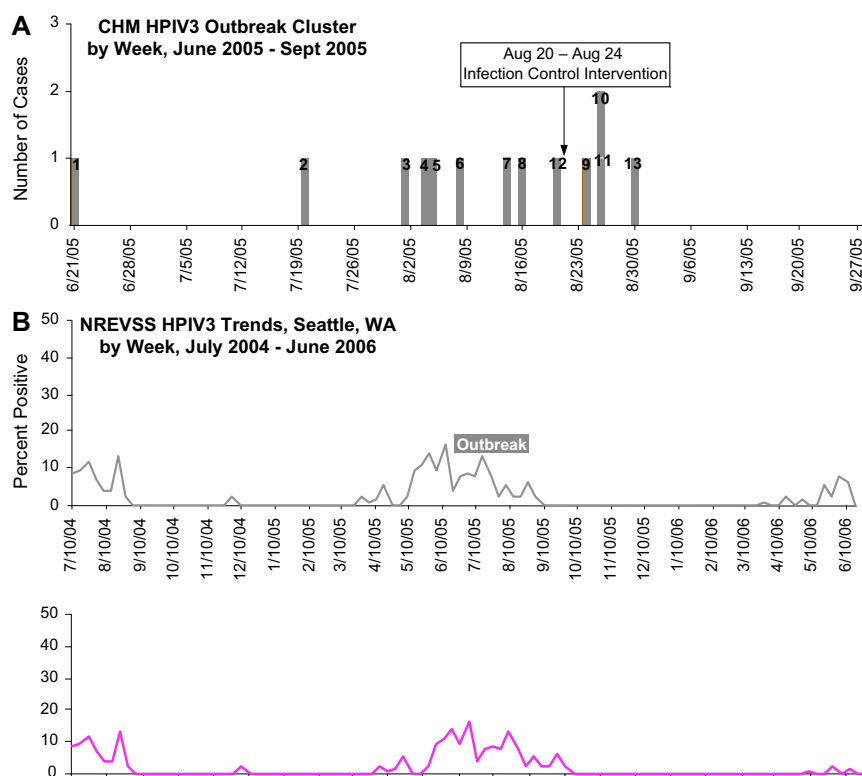


Figure 2. HPIV3 outbreak in the HSCT OPC. (A) temporal distribution of HPIV3 outbreak cases. (B) CDC NREVSS weekly percentage of HPIV3 cultures positive for Seattle surveillance sites showing the HSCT OPC outbreak in the inset.

HPIV3 activity, outbreaks in immunocompromised hosts do not typically follow a seasonal pattern, and that nosocomial spread can be multiseasonal, as well as rapid and prolonged [18-23]. Thus, it seems likely that control measures introduced in the outpatient HSCT clinic played some role in curtailing the epidemic.

The outcome of patients in this nonrandomized study is noteworthy. As detailed in Table 1, 4 patients with URTI were not treated and recovered. Eight patients presented with established LRTI; of these, 4 were treated with ribavirin and died, and 1 was treated with ribavirin and recovered. Of the 3 patients with LRTI who were not treated with ribavirin, 1 died and 2 recovered. Finally, 1 patient was treated with ribavirin very early in the course of probable LRTI and recovered. Although not controlled, these data suggest no benefit to aerosolized ribavirin in treatment of patients with established LRTI and accentuate the critical need for interventions to prevent transmission and better therapeutic modalities. Well-designed clinical trials exploring this complicated area would be useful to help guide interventions, but this is likely unfeasible because of the relative infrequency of these events. Thus, we conclude that the development and adherence of strict isolation policies for patients, family members, and care providers with active respiratory infections may be the best available intervention.

In summary, 13 patients with HPIV3 infection associated with significant morbidity and mortality

were identified in the HSCT population at our academic medical institution over a several months. Based on genetic relatedness as well as demographic and exposure history, in the majority of these cases acquisition of HPIV3 likely occurred in the HSCT OPC. Prompt attention and focus on infection control interventions was associated with a rapid decrease in the number of incident cases. Policies and procedures addressing the approach to patients with respiratory viral illnesses in HSCT OPC populations should be formulated and reinforced with clinic staff to help prevent the spread of these infections. Given the possibility of asymptomatic or prolonged viral shedding of HPIV3, the paucity of documented effective treatment strategies, the high mortality, and the emergence of newly identified viral respiratory pathogens (eg, bocavirus, coronaviruses), such infection prevention policies should emphasize high vigilance and strict respiratory etiquette throughout the year. A larger prospective control study would be useful to better clarify the role of infection control practices for HPIV3 infection in HSCT recipients.

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